IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mar Tormo
Ana M. Tari
Gabriel Lopez-Berestein

Serial No.: 08/726.211

Filed: October 4, 1996

For: INHIBITION OF BCL-2 PROTEIN EXPRESSION BY LIPOSOMAL ANTISENSE OLIGODEOXYNUCLEOTIDES

Group Art Unit: 1636

Examiner: R. Schwartzman

Atty. Dkt. No.: UTXC:504/STA

Considered
KAL 01-29-01

CERTIFICATE OF HAND DELIVERY

I hereby certify that this correspondence is being hand delivered for filing to: Examiner R. Schwartzman Group 1636, Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

Date _____ Signature _____

DECLARATION OF DR. RICHARD J. FORD

I, Richard J. Ford, hereby declare as follows:

1. I am a professor in the Department of Anatomic and Molecular Pathology at The University of Texas M.D. Anderson Cancer Center, Houston, Texas where I am Chief of the Section of Pathology. I received an M.D. from Case Western Reserve University in Cleveland, Ohio and a Ph.D. from Washington University in St. Louis, Missouri. I have had extensive experience in the study and treatment of cancer and lymphomas, including those that are related to the onset of AIDS, and am familiar with various animal models useful in developing treatments for cancer. I have published more than fifty articles and chapters in books in the area

of cancer research. References containing examples of my work are included in my *Curriculum Vitae*. A copy of my *Curriculum Vitae* is attached as Exhibit 1.

2. I understand that the patent examiner in charge of assessing the patentability of the above-referenced application has rejected the claims of that application. I have reviewed the specification, pending claims, and an inventors' declaration with additional supporting data. I am providing this declaration to submit additional information relating to this application. I am also familiar with the work of Dr. Gabriel Lopez-Berestein through our mutual affiliation with The University of Texas M.D. Anderson Cancer Center.

3. The nude mouse has been used in experimental and clinical research since it was first described in 1969 (Rygaard and Povlsen, 1969, attached as Exhibit 2). It is generally accepted that the nude mouse model is the best indication of what can be expected from human trials. There are numerous studies that support that transplants of human tumors into the nude mouse provide an accepted model for testing the clinical efficacy of anticancer agents (Inoue *et al.*, 1983; attached as Exhibit 3, Guiliani *et al.*, 1981; attached as Exhibit 4, Giovanella *et al.*, 1983; attached as Exhibit 5, Tashiro *et al.*, 1989, attached as Exhibit 6, Khleif and Curt in *Cancer Medicine,* 4th Ed., pp. 855-68, 1997, attached as Exhibit 8). Positive results from nude mouse studies indicate a reasonable expectation of positive results in clinical trials.

4. The nude mouse has been used to screen for, study and confirm anticancer effects of numerous agents. Literature supports the concept that doses of compounds used in preclinical animal studies can be correlate to studies in human clinical trials (Tashiro *et al.*, 1989, attached as Exhibit 6).

5. Correlation between the nude mouse and human clinical responses to, for example, cyclophosphamide, 1-(4-amino-2-methylpyrimidin-5-yl)-methyl-3-(2-chloroethyl)-3-nitrosurea hydrochloride, vinblastine and 5 fluorouracil have been shown. Further, other studies used BALB/c nude mouse model for human breast cancer to evaluate the antitumor activity of a variety of drugs, including vincristine, vinblastine vindesine, dauonomycin, mitoxantrone, and 5

fluorouracil amongst others (Inoue *et al.*, 1983, attached as Exhibit 3). These studies showed good correlation between anticancer activity of various drugs in the nude mouse model for human breast cancer and in clinical treatment in humans. In yet another comprehensive study (Guiliani *et al.*, 1981, attached as Exhibit 4), BALB/c nude mice were transplanted with breast, colon, lung, melanoma, ovarian prostate and larynx cancers and the effects of doxorubicin on these cancer models was studied. It was found that in each case the results from the model studies correlated extremely well with clinical data.

6. The National Cancer Institute has even employed a development scheme in assaying for *in vivo* antitumor activity in which the human tumor cell line most sensitive to an active candidate *in vitro* is tested as a xenograft in a subcutaneous implant site in a nude mouse (*Cancer: Principles & Practice of Oncology,* 5th Ed., 1997, pp. 392-94, attached as Exhibit 7).

7. The use of severe combined immunodeficiency (SCID) mice allows for transplantation of normal and malignant human hematological cells (Flavell, 1996, attached as Exhibit-9). The SCID mouse model has also been employed in the art to predict therapeutic benefits of antisense therapy in SCID mice bearing human leukemias and lymphomas (Flavell, 1996, attached as Exhibit 9).

8. The above studies demonstrate that the mouse model emulates the clinical situation in a number of cancers including, lung, breast and ovarian cancers, leukemias and lymphomas. Furthermore, predictions from the nude and SCID mouse model studies have correlated well with clinical studies.

9. The present application refers to the treatment of BCL-2-associated diseases using liposomal formulations of antisense BCL-2 oligonucleotides. SCID mouse models that possessed follicular lymphoma were treated with such formulations.

10. Nude and SCID mice data are often predictive of responses in human trials. This confirms that one could use the methods, compositions and kits described in the specification to

treat patients having a BCL-2 associated disease. It is my opinion that, a review of the mice data in the previous declaration provides a practitioner sufficient guidance to prepare a protocol to practice the claimed invention.

11. One skilled in antisense therapy will be able to take the teachings of the specification and employ neutral liposomal formulations of antisense BCL-2 oligonucleotides to treat cancer and other BCL-2-associated diseases.

12. I declare that all statements made of my knowledge are true and all statements made on the information are believed to be true; and, further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereupon.

Date: 6/10/98

Richard J. Ford, M.D., Ph.D.